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(54) [Title of the invention] A gas permeable material with excellent hemocompatibility

(57) [Abstract]

[Objective] to provide a method for producing a material which remains gas permeable and hemocompatible over extended periods of time, can be easily made into thin films, and suitable for use with artificial hearts and lungs without causing wet lungs.

[Composition] A polyurethane or polyurethane urea characterised in that it is obtained from at least the following reactants: a polysiloxane containing a terminal hydroxy or amino group that can react with the diisocyanate or isocyanate group, a polyether polyol containing a tertiary amino group, said tertiary amine being quaternised[1] with an alkyl halide or an activated ester, or treated with a heparin, and the total number of carbon atoms of the two alkyl groups bonded to the quaternary chlorinated nitrogen is in the range from 7 to 16.

[CLAIMS]

[Claim 1] A gas permeable material with excellent hemocompatibility characterised in that it is a polyurethane or a polyurethane urea obtained by reacting a polysiloxane (NOPS) containing a terminal hydroxy or amino group that can react with the diisocyanate (DI) or isocyanate group, a polyether polyol (NPO) containing a tertiary amino group, and if necessary another polyamine or polyol wherein part or all of the tertiary amino group contained in said polyurethane or polyurethane urea is quaternised by an alkyl halide or an activated ester, and the total number of carbon atoms contained in the side chain groups bonded to the quaternary chlorinated nitrogen is in the range from 7 to 16.

[Claim 2] A gas permeable material with excellent hemocompatibility as claimed in claim 1, characterised in that said NPO contains more than 50 mol % of an amine diol shown by the formula 1 below.

[Claim 3] A gas permeable material with excellent hemocompatibility characterised in that it is obtained by further treating the material claimed in claim 1 and 2 with a heparin.

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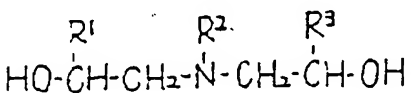
[1] Translator's note: This verb refers to a process in which a tertiary amino group is converted

Formula 1



in which R^1 and R^3 are a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms, and R^3 is an alkyl group containing from 1 to 10 carbon atoms.

[Detailed description of the invention]

[0001]

[Field of utilisation in industry] The present invention relates to a material used as a component of the oxygen exchange film of a gas exchange device such as that used in an ECMO (Extracorporeal film oxygenator), a lung-heart machine, artificial lungs used as substitutes for the lungs of a lung disorder patient, and devices used in open heart surgery in operations of the heart to maintain blood circulation and oxygen supply.

[0002]

[Prior art] The gas exchanger (the device which adds oxygen to and removes carbon dioxide from the blood to "convert" veins into arteries) of lung-heart machines that are currently available on the market belongs to one of the following three types, depending on the method for adding oxygen: (1) Gas-blood direct contact type (bubble type, film type etc.); (2) type in which gas exchange is carried out through small holes (whose diameter ranges from hundreds to thousands of Angstroms) and includes the hollow fibre type, the laminated type etc. (3) Gas diffusion type (in which the gas is dissolved, diffused to and passed through a homogeneous film).

[0003]

[Problems to be solved] Among said prior art devices, (1) converts oxygen into bubbles then directly blows them into the veins. When this method is used, as blood and oxygen gas are in direct contact, erythrocyte membranes are broken, causing the number of free hemoglobins to increase, which facilitates hemolysis.

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into a quaternary group by treatment with a suitable agent, i.e., an alkyl halide.

In addition, since oxygen gas is directly blown into the veins, the gas remains in the blood as fine bubbles. It is very difficult to remove these fine bubbles and blood may be severely damaged. For these reasons the device cannot be used as a substitute to carry out the functions of the heart and lungs over extended periods of time.

[0004] When a device of type (2) is used, gas exchange is carried out through small holes, and there is no direct contact between blood and the gas as when a device of type (1) is used, and problems involving blood damage and admixture of gas bubbles with blood are thus solved. However, as gas exchange is carried out through small holes, the moisture in blood and the components of the plasma ooze out, and as a result the gas exchange efficiency is lowered with time. Moreover, the most common material used in these films is polypropylene or a similar product, which has poor hemocompatibility. In other words, if these materials are used, factors causing blood coagulation and complements are activated, and thrombocytes and leucocytes tend to coagulate or fuse together. In order to suppress these reactions it is necessary to administer a large amount of an anti-coagulant such as heparin. On the other hand, administering a large amount of heparin tends to cause bleeding and may be life endangering. For these reasons, gas exchange devices of type (2) cannot be used over extended periods of time as they frequently cause disorders of internal organs due to bleeding and damage to blood cells.

[0005] If a device of type (3) is used, gas exchange is carried out through the boundaries of a homogeneous film, problems caused by a device of type (1) such as damage to blood cells and admixture of gas bubbles with blood do not arise, and the disadvantage - oozing of moisture and plasma components- that a device of type (2) involves does not arise either. This type of film is normally made of a silicon rubber (silicon-based polymer). It is known that silicon rubber is superior to other materials regarding hemocompatibility. Therefore, among gas exchangers of the types (1) to (3), those of type (3) are considered most suitable. However films of this type also have shortcomings. (a) Silicon rubber, when used alone, is of low strength and it is necessary to use thick films or fillers as reinforcing agents to achieve a desired strength. As a result gas diffusion is slowed down and oxygen exchange efficiency is low; (b) As the hemocompatibility of silicon rubber is still inadequate, blood coagulation still occurs, and

consequently, administration of a substantial amount of heparin is required, resulting in frequent bleeding and is thus life endangering; (c) As complements are activated, the blood coagulation system is altered, the vessel walls are more permeable to leucocytes and lymphocytes, causing an increase in the number of leucocytes, wich may lead to life endangering phenomena such as fever, shocks, and delays in post operation recovery. Lung-heart machines that have this gas exchange device can be used over a period of only 2 to 3 days at most, and if the device is used for more than the above mentioned period, the survival rate is almost nil.

[0006] Materials that can be used in place of silicon rubber films of type (3) such as the following polymers are being studied. (a) As an example of reinforcing films, US patents Nos. 3419634 and 3419635 describe the manufacture of silicone-polycarbonate copolymers. In addition US patent No. 3767737 describes a method for producing films using said copolymers. Japanese patent No. Sho 61-430 describes selectively gas-permeable films made from a polyurea obtained by reacting a diamino polysiloxane and an isocyanate compound with a polyvalent amine. In addition, the detailed description of Japanese patent No. Sho 60-241 567 [Basic Polymer Technology Research Team No. PM-80] discloses selectively gas-permeable films made from a polyurethane urea obtained by reacting a diamino polysiloxane, and an isocyanate compound with a polyvalent hydroxyl compound containing a tertiary nitrogen atom. These polymers of are relatively strong but still inadequate as far as hemocompatibility is concerned, and are not a solution the problems (b) and (c). Moreover, since the polymers mentioned in the detailed description of said Japanese patents Nos. Sho 61-430 and Sho 60-241 567 contain two types of bonds, the siloxane and urea bonds, which are of different polarities, it is very difficult to select a suitable solvent to dissolve them and to shape them into thin films.

[0007] In order to solve the problems concerning blood coagulation mentioned in (b), Polymer Report No. 36 223 (1979) has proposed products obtained by bonding a heparin,[2] through ionic bonds, with certain polymers. The polymers used are cross-linked polymers obtained by quaternising the tertiary amino groups of the copolymers formed from three compounds: dimethylaminoethyl-

[2] Translator's note: Refer to a later paragraph [0028[which defines the term "heparin/s".

methacrylate, methoxypolyethyleneglycom methacrylate and glycidyl methacrylate, then blending with them with a polyurethane, and subjecting the mixture to thermal treatment. Since the heparin is slowly released from the surface of articles shaped from these materials, blood coagulation is thus prevented. However their hemocompatibility is not yet sufficient, and therefore they cannot be used in lung-heart machines. Japanese patent No. Sho 58-188458 discloses an anti-thrombosis elastomer which is a polyurethane or polyurethane urea which contains a polysiloxane unit in the skeleton. This elastomer, however, does not exhibit an adequate thrombosis resistance. Moreover, it is not sufficiently gas-permeable, and the activity of its complements is not controlled. For these reasons it cannot be used for the aforementioned purposes.

[0008] Materials that can be used to solve problems involved in controlling the activity of complements mentioned in (c) are widely used in permeable films in artificial dialysing kidneys. For example, it has been reported in *Jinko Jinzo*[3] 16 (2), 818-821 (1987) that in films obtained by diethylaminoethylating cellulose films, the activity of complements is remarkably suppressed during dialysis compared with the initial films. However, since these films exhibit poor gas permeability, they cannot be used as materials for producing films used in artificial lungs.

[0009] In addition, Japanese patent No. Sho 54-18518 discloses a material which has a negative standard membrane potential and can be used as anticoagulant films in medical instruments. The material is obtained from a copolymer. which has a hydrophilic portion, a hydrophobic portion and a quaternary ammonium salt as their essential units, and a heparin. However, this material does not have a gas permeable segment, it is not gas permeable at all. Even if a gas permeable segment is introduced into the copolymer, as mentioned in the detailed description, the cationic copolymer has a moisture content ranging from 5 to 80% when it coexists with water. Water and plasma can penetrate films made from this copolymer (a phenomenon known as "wet lungs"), which results in a lowered gas permeability and as active ingredients leak into the body, it is difficult to maintain life of the living body.

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[3] Translator's note: "Artificial kidneys".

[0010]

[Means used to solve the problems] The present invention aims at overcoming the shortcomings of the prior art. Its objective is to provide a material which exhibits gas permeability over extended periods of time without inducing "wet lungs', excellent hemocompatibility, can be easily shaped into thin films, and there fore is suitable to produce films used in the gas exchange device of lung - heart machines.

[0011] The gas permeable material with excellent hemocompatibility according to the invention is characterised in that it is a polyurethane or a polyurethane urea obtained by reacting a polysiloxane (NOPS) containing a terminal hydroxy or amino group that can react with the diisocyanate (DI) or isocyanate group, a polyether polyol (NPO) containing a tertiary amino group, and if necessary another polyamine or polyol, wherein part or all of the tertiary amino group contained in said polyurethane or polyurethane urea is quaternised with an alkyl halide or an activated ester, and the total number of carbon atoms contained in the side chain groups bonded to the quaternary chlorinated nitrogen is in the range from 7 to 16. " The number of carbon atoms contained in the side chain groups" as used herein refers, in the case of formula 1, to the total of the number of carbon atoms contained in R2 and those contained in the quaternising agent, said total being preferably in the range from 7 to 16. The gas permeable material with excellent hemocompatibility according to the invention is characterised in that it is obtained by polymerising said tertiary amino group containing polyether polyol in the presence of more than 50% of an aminediol shown by formula 1. The gas permeable material with excellent hemocompatibility according to the invention is characterised in that it is obtained by treating the polyuerethane or polyuretane urea with a heparin.

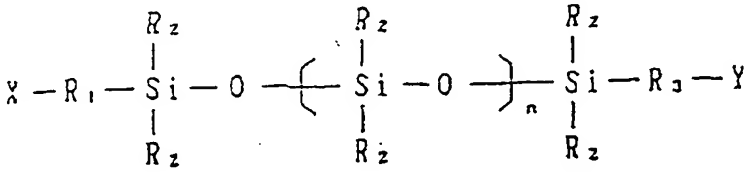
[0012] As the diisocyanate used in the polyurethane or polyurethane urea, which is the gas permeable material with excellent hemocompatibility according to the invention, (aromatic, aliphatic or alicyclic) diisocyanates that are usually used in the preparation of polyurethanes or polyurethane ureas can be used. Said aromatic diisocyanates include aromatic diisocyanates containing from 8 to 25 carbon atoms such as p-phenylene diisocyanate, o- phenylene diisocyanate, m- phenylene diisocyanate, 2,4-tolylene diisocyanate, 2,6- tolylene diisocyanate, xylylene diisocyanate, 4,4'-diphenylmethane diisocyanate, 4,4'-diphenylpropane

diisocyanate, naphthalene diisocyanate; aliphatic diisocyanates include aliphatic diisocyanates containing from 6 to 20 carbon atoms such as hexamethylene diisocyanate, heptamethylene diisocyanate, octamethylene diisocyanate, nonamethylene diisocyanate, decamethylene diisocyanate; alicyclic diisocyanates include alicyclic diisocyanates containing from 8 to 20 carbon atoms such as 4,4'-dicyclohexylmethane diisocyanate, isophorone diisocyanate. A mixture of more than two different isocyanates may be used. As components of the polymers of the invention, mixtutes of more than two polysiloxanes and polyether polyols containing a tertiary amino group may be used.

[0013] Preferably, the polysiloxane which contains a terminal hydroxy group or amino group that can react with the isocyanate group is a compound shown by formula 2:

[0014]

Formula 2



[0015] (In formula 2, each of X and Y is -OH, NH2 or a substituted amino group containing from 2 to 10 carbon atoms; each of R1 and R3 is an alkylene group, oxyalkylene group, or an aralkylene group containing from 2 to 10 carbon atoms; each of R3 is an alkyl group, aryl group or an aralkyl group containing from 1 to 10 carbon atoms; n is an integer ranging from 5 to 300). : min 7 repeat units.

[0016] The molecular weight of the polysiloxane is in the range from 200 to 20 000, preferably from 500 to 8000, and more preferably from 1000 to 4000.The content of the polysiloxane in the polyurethane or polyurethane urea obtained is in the range from 20 to 90%, preferably from 30 to 85%.

[0017] The polyether polyol containing a tertiary amino group (NPO) used in the present invention is obtained by polymerising the aminediol shown by formula 1 in the presence of a strong acid catalyst. It is desirable that an aminediol with the total number of carbon atoms contained in R1, R2, and R3 ranging from 2 to 10, preferably, from 3 to 8, be used. If the total number of carbon atoms was less than 3, the final product would be excessively hydrophilic, water and

plasma would pass through it easily, and as the product would excessively water absorbing, and even the product was heparinized after being quaternised, the heparin[4] would be rapidly released and hemocompatibility would not be retained over a long period. On the contrary, if the total number of carbon atoms exceeded 10, steric hindrance around the nitrogen atom of the amino group would be increased, and it would be difficult to quaternise the product. Even if the product could be quaternised; again, due to steric hindrance, the bonds formed with heparin would be weak leading to weak "heparinization". and long term hemocompatibility would be difficult to achieve. Finally, R1, R2 and R3 are preferably linear alkyl groups.

[0018] Amine diols that are most suitable for the purpose of the invention include 3-ethyl-3-aza-1,5-pentanediol, 3-propyl-3-aza-1,5-pentanediol, 3-butyl-3-aza-1,5-pentanediol, 1,5-pentanediol, 3-pentyl-3-aza-1,5-pentanediol, 3-hexyl-3-aza-1,5-pentanediol, 3-heptyl-3-aza-1,5-pentanediol, 3-octyl-3-aza-1,5-pentanediol, 3-decyl-3-aza-1,5-pentanediol, 4-methyl-4-aza-2,6-heptanediol, 4-ethyl-4-aza-2,6-heptanediol, 4-propyl-4-aza-2,6-heptanediol, 4-butyl-4-aza-2,6-heptanediol, 4-heptyl-4-aza-2,6-heptanediol, 4-octyl-4-aza-2,6-heptanediol. Strong acids that can be used as catalyst include phosphorous acid, hypophosphorous acid, pyrophosphoric acid, p-toluenesulphonic acid, methanesulphonic acid. These acids are used in a proportion of from 0.01 to 8 mol%, preferably from 0.1 to 3 mol%.

[0019] In addition to the aminediol shwon by formula 1, other diols may also be used if necessary. Such diols include aliphatic or alicyclic diols containing from 2 to 20 carbon atoms and/or polyoxyalkylene glycols having a molecular weight ranging from 500 to 2000. Examples of said aliphatic or alicyclic diols are ethylene glycol, propylene glycol, butanediol, neopentyl glycol, cyclohexane dimethanol etc. Examples of said polyoxyethylene glycols are polyethylene glycol, polypropylene glycol, polytetramethylene glycol, etc. Naturally, DI, NOPS, NOP and other diols are to be selected within the scope of the present invention.

[0020] The aminopolyether polyol is synthesised as follows. Firstly, other diols are mixed with the aminediol shown in formula 1, said catalyst is added to the mixture and the whole is heated under normal pressure to 150 to 270°C, pref-

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[4] Translator's note: Refer to the definition of "heparin/s" (in paragraph [0028].

erably to 200 to 250°C to remove the water formed and the reaction is allow to proceed for 1 to 30 hours, preferably for 3 to 20 hours. Subsequently, the pressure is reduced in 0.5 to 6 hours, preferably in 1 to 4 hours, to less than 10 mmHg, preferably, less than 3 mm Hg. The reaction is allowed to proceed for another 1 to 10 hours, preferably 2 to 7 hours to yield the aminopolyether polyol which has a molecular weight in the range from 200 to 8000, preferably from 500 to 4000. The content of basic nitrogen of this aminopolyether polyol is 1.0 to 15.0%, preferably 2.0 to 11.0%. In the synthesis of the polyurethane or the polyurethane urea according to the invention, the aminopolyether polyol is used in such a proportion that the amino group in the molecule of the polyurethane or the polyurethane urea is from 0.01 to 3.00 mmol/g, preferably from 0.05 to 2.00 mmol/g.

[0021] In the synthesis of the polyurethane or polyurethane urea according to the invention, the other diols or polyamines, which are used if necessary, are low molecular weight chain extenders or high molecular weight polyols. Low molecular weight chain extenders include diols, diamines and oxyalkylene glycols. Said diols include aliphatic and/or alicyclic diols containing from 2 to 20 carbon atoms such as ethylene glycol, propylene glycol, 1,4-butanediol, neopentyl glycol, 1,5-pentanediol, 1,6-hexanediol, 1,4-cyclohexane dimethanol, 1,3-cyclohexane dimethanol. Said diamines include aliphatic and/or aromatic diamines such as ethylene diamine, propylene diamine, 1,4-tetramethylene diamine, 1,6-hexamethylene diamine, 1,4-diaminocyclohexane, 4,4'-diaminodiphenylmethane, xylylene diamine.

[0022] Said oxyalkylene glycols include those containing from 5 to 30 carbon atoms such as diethylene glycol, triethylene glycol, tetraethylene glycol, dipropylene glycol, tripropylene glycol, and/or tetrapropylene glycol. Among these low molecular weight chain extenders, ethylene glycol, 1,4-butanediol, 1,6-hexanediol, neopentyl glycol, ethylene diamine, propylene diamine, 1,4-butylene diamine and 1,6-hexamethylene diamine are particularly preferred. Said high molecular weight polyols include polyoxyalkylene glycols and polyester diols. Polyoxyalkylene glycols include polyethylene glycol, polypropylene glycol, polytetramethylene glycol having a molecular weight ranging from 300 to 15000, preferably from 800 to 8000. Polyester diols include polyester diols obtained from an aliphaticdiol containing 2 to 10 carbon atoms and an alphatic

carboxylic acid containing from 6 to 16 carbon atoms; polyester diols obtained from a caprolactone such as ε- caprolactone.5 Among these high molecular weight polyols polyester diols are particularly preferred. The content of the high molecular weight polyol in the final polymer is less than 50%, preferably less than 30%.

[0023] The polyurethane and polyurethane urea according to the invention can be both synthesised by conventional methods. For example, the polyurethane is synthesised according to the solution polymerisation method as follows. A polysiloxane having a terminal hydroxy or amino group (formula 2), and an diisocyanate and if necessary, one of said high molecular weight polyols, are dissolved in a solvent which is inert to the isocyanate group, and the solution is stirred under a nitrogen atmosphere at 30 to 150°C, preferably, 40 to 120°C, for 5 to 300 minutes, preferably for 5 to 120 minutes to allow the reaction to proceed. Said aminopolyether polyol (NPO) and, if necessary one of said low molecular weight chain extenders (low molecular weight diol) are added, and the reaction is allowed to proceed at 0 to 100°C, preferably 5 to 80°C, for 15 to 300 minutes to extend the chains and obtain the polymer.

[0024] Solvents that can be used include dioxane, tetrahydrofuran, chloroform, carbon tetrachloride, benzene, toluene, acetone, methyl ethyl ketone, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, and their mixtures. In particular, dioxane, tetrahydrofuran, methyl ethyl ketone, N,N-dimethyl formamide, N,N-dimethyl acetamide, and their mixtures are preferred. During the reaction time a polymerisation catalyst is added if necessary. Catalysts include tin-based catalysts such as dibutyltin dilaurate, titanium-based catalysts such as tetrabutoxy titanium, and other metal catalysts. The catalyst is added at a concentration of from 1 to 500 ppm, preferably from 5 to 100 ppm. To synthesise the polyurethane by solution polymerisation, said monomers can be introduced at the same time.

[0025] In said polymerisation reaction the mixing ratios of the components are as follows: the mole ratio of the polysiloxane polyol versus the aminopolyether polyol is in the range from 100/1 to 1/3, preferably from 20/1 to 1/5; the mole ratio of [the polysiloxane polyol and the aminopolyether polyol] (namely, NOPS

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[5] Translator's note: ε- caprolactam ?

+ NPO) versus (if necessary used) the polyol which is the chain extender is 1/100 to 1/1, preferably 1/30 to 1/2; the mole ratio of all the polyols versus the diisocyanate is 10/8 to 8/10, preferably 10/9 to 9/10.

[0026] The polyurethane urea according to the invention can be synthesised by any of the conventional methods. Among these methods, solution polymerisation is particularly preferred. The polyurethane urea is synthesised according to the solution polymerisation method, using a polysiloxane polyol, an aminopolyether polyol and if necessary, a high molecular weight polyol. These compounds are dissolved in a solvent inert to the isocyanate group. The solution is allowed to react, as in the case of the polyurethane at 0 to 150°C, preferably, 0 to 100°C, for 5 to 300 minutes, preferably for 5 to 120 minutes. The reaction solution is then cooled to 0 to 40°C, preferably to 5 to 20°C, and then the polysiloxane having a terminal amino group (formula 2), and if necessary a low molecular weight chain extender (low molecular weight diamine) are dissolved in the inert solvent and the resulting solution is dropped onto the reaction mixture, and the reaction is allowed to proceed to yield the polyurethane urea having the desired molecular weight. In this reaction, since the polymer formed contains urea bonds, it is desirable to use an amide-based solvent such as N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, or a mixed solvent formed from these solvents with dioxane or tetrahydrofuran. It is also desirable that a salt such as LiCL, LiBr or CaCl36 be used to increase the solubility of the polymer formed. The ratios of the components and other conditions are based on those applied in the case of the polyurethane.

[0027] The polyurethane or polyurethane urea obtained in this manner is shaped into hollow threads or films and used as gas permeable material in lung-heart machines. It is necessary to quaternise the polyurethane or polyurethane urea and to bond it with heparin or a similar compound (hereafter referred to as heparins). In this manner its hemocompatibility is further enhanced. The polyurethane or polyurethane urea is treated with a quaternising agent to quarternise its tertiary nitrogen atom, then treated with a heparin. A polyion complex thus formed contains bonds with the heparin. As the quaternising agent/s, a least one of the following compounds is used: alkyl halides, aralkyl halides, aryl

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[6] Translator's note: $CaCL_2$?

halides and activated esters containing 1 to 10 carbon atoms, preferably 2 to 8 carbon atoms. Among these quaternising agents, alkyl halides containing 1 to 10 carbon atoms, preferably 2 to 8 carbon atoms, are most suitable. The quaternising agent/s is/are used in a mole ratio of 0.1 to 10.0, preferably 0.5 to 5.0, with respect to the tertiary amino group. The polyurethane or polyurethane urea is quaternised either by dissolving it in a suitable solvent, adding one of said quaternising agents into the resulting solution and allowing the reaction to proceed; or shaping the polymer then allowing it to come into contact with a solution of said quaternising agent. The method involving a reaction in solution is preferred. For example, a quaternising agent is added to the solution of the polyurethane or polyurethane urea as soon as the polymerisation reaction is complete, and the reaction is allowed to proceed at 10 to 100°C, preferably 40 to 80°C, for 1 to 60 hours, preferably 1 to 30 hours. In this manner the yield of the quarternising reaction of the tertiary amino group is 1 to 100%, preferably higher than 10%.

[0028] The polyurethane or polyurethane urea containing a quaternised amino group can be shaped into articles, as desired, as films or hollow threads. The shaped articles are brought into contact with a heparin to form bonds with the latter (this process is called "heparinisation"). For example, the shaped articles made from said polyurethane or polyurethane urea containing the quaternised amino group are heparinised by immersing them into an aqueous solution (using a mixed solvent of a water soluble solvent such as dimethyl formamide, dimethyl acetamide, tetrahydrofuran or ethanol, and water) at 20 to 100°C, preferably 40 to 80°C, for 0.1 to 40 hours, preferably 0.5 to 30 hours. The term "heparins" as used herein refers to natural or synthetic polymers containing the $-SO_3H$ group, or the $-NHSO_3$ group such as heparin, chondroitin sulphuric acid etc.

[0029] The polyurethane or polyurethane urea according to the invention is made into hollow threads of hollow thread films by a conventional method. Alternatively the material is dissolved in a suitable solvent, and the resulting solution is flowed on a flat plate and dried to give a thin film. If necessary, said process of heparinisation is carried out to give the desired gas permeable material. If this material of the invention is used as an oxygen exchange film in lung-heart machines, oxygen/carbon dioxide gas exchange is efficiently carried out. Addi-

tionally, as its hemocompatibility is excellent, it would be very difficult for blood coagulation or shock symptoms induced by activation of complements to occur. When the heparinised material is used, the heparin is very slowly released onto the polymer, and coagulation resistance is further enhanced. Thus, the material according to the invention can be efficiently used over extended periods of time in lung substitutes such as ECMO. Moreover the material according to the invention can be used as oxygen enriching medical films or oxygen enriching films used in gas burning in inhalation treatment of respiratory disease patients. The material is also recommended for use as coating material for medical instruments in contact with blood by virtue of its anti-thrombosis characteristics.

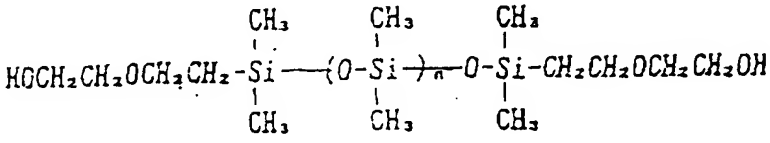
[0030]

[Examples] The invention will be now explained in detail by way of examples. In the examples, "parts' means "parts by weight".

[Example 1] 4-methyl-4-aza-2,6-pentanediol (1472 parts), 1,6-hexanediol (591 parts) and phosphorous acid (12.3 parts) were placed into an autoclave and the mixture was stirred and heated under a nitrogen stream at 200 ~ 220°C under constant pressure for 26 hours to allow the reaction to proceed while removing the water formed by distillation. Subsequently, the pressure was reduced in 2 hours at 220°C from 760 mmHg to 0.3 mmHg, and the reaction was continued for another 3 hours at 220°C under 0.3 mmHg. In this manner an aminopolyether polyol (a) with an OH value of 57.3 and a basic nitrogen value of 6.11 mmol/g was obtained. A polydimethylsiloxanediol (1800 parts) shown by the formula 3,7

[0031]

Formula 3



[0032] said aminopolyether polyol (a) (300 parts), 1,4-butanediol (90.1 parts), dibutyltin dilaurate (0.3 part) and 4,4'-diphenylmethane diisocyanate (hereafter shortened to MDI, 554 parts) were dissolved in a mixed solvent of tetrahydrofu-

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[7] Translator' note: The "break" here is unnatural. Please note that the first word of [0032] ("said") is in lower case.

ran (hereafter shortened to THF, 1994 parts) and dimethylformamide (hereafter shortened to DMF, 3887 parts) and the reaction was allowed to proceed under a nitrogen stream at 40°C for 1 hour, then at 60°C for 15 hours. In this manner a base polymer solution A, with a solid content of 32% and a viscosity of 3200 poise (at 30°C), was obtained. DMF was added to this solution and stirred to give a 5% solution. This 5% solution (10 g) was uniformly applied onto a horizontally maintained 100 cm2 glass plate which was then dried at 40°C for 1 hour and then at 60°C for 2 hours under a nitrogen stream, and finally under reduced pressure for 15 hours to give a 50 μm thick base polymer film A.

[0031] Subsequently, hexyl iodide (4.58 parts) was added to a 10% base polymer solution (100 parts), which had been obtained by diluting said base polymer film A with DMF, and the reaction was allowed to proceed at 70°C with stirring to quaternise the tertiary amino group of the base polymer. The solution was then diluted with dioxane to give a 5% solution, which was then treated in the same manner as said base polymer A to give a 50 μm thick quaternised polymer film A. Accurately weighed amounts (0.2 g) of the base polymer film and the quaternised base polymer A were dissolved in 50 ml of a mixed solvent of dioxane/ethanol (7:3 vol/vol). A N/10 solution of $HClO_4$ in dioxane was dropped into the above solution using a potentiometric titrimeter (Hiranuma Corp., Model Comtite-7), and the content of basic nitrogen was determined from the inflection point. It was found that the content of basic nitrogen of the base polymer film A was 0.67 mmol/kg and that of the quaternised film A was 0.25 mmol/kg. From these results the quaternisation yield was calculated to be approximately 63%. The permeability coefficient of oxygen against the film was determined by a gas permeability measuring device (Yanagimoto Corp), and it was found that the oxygen permeability coefficient of the base polymer A was $3.35X10^{-8}$ cm3 (STP) cm/cm2.sec.cmHg, and that of the quaternised film A was $8X10^{-8}$ (hereafter the unit cm^3 (STP) cm/cm^2.sec.cmHg will be omitted). Subsequently, the films wee immersed in a 1% aqueous solution of heparin to heparinize the films for 2 hours at 70°C to give heparinized base polymer film A and heparinized quaternised polymer film A. These films were cut into circles 3 cm in diameter which were soaked in a physiological sodium chloride solution for one week, then thoroughly washed with water and the water on the surface of the film was

sucked with filter paper. The film was stuck onto the centre of a watch glass 10 cm in diameter. Citrated plasma from a rabbit (Japanese white rabbit) (200 µl) was placed on the film, then a 1/40 M aqueous solution of calcium chloride (200 µl) was added. The watch glass was floated on a constant temperature water bath, then the solution in the watch glass was manually and thoroughly stirred and the time elapsing from the moment when calcium chloride was added until coagulation occurred (the moment when the plasma stopped moving) was measured. The duration was independently determined for glass as reference, and subtracted from the above time. The result was used a relative value.

[0034] Each solution was diluted with DMF to 1%, then glass beads (40~60 mesh) were immersed in each of them (100 ml) for 30 minutes. The resulting mixture was filtered with a glass filter and the glass beads were dried at 40°C under a nitrogen stream for 3 hours, and under reduced pressure at 60°C for 12 hours. The surface of the glass beads was coated with each of the polymers. The glass beads (200 mg), Veronal buffer solution and plasma (pool plasma from a healthy person) were placed in a plastic test tube which was gently vibrated at 37°C, and incubated for 30 minutes. The haemolytic complement units and the (abbreviated as CH_{50}) and the amounts of C3a and C5a formed were measured and the resuts are shown in Table 1. The CH_{50} was determined according to the Meyaer method (Neyer, M. M., "Complement and Complement Fixation", Experimental Immune Chemistry, 2nd Edition, p. 133, Charles C, Thomas Publisher, Stuttgart, 1964), and the C3a and C5a were measured using a radio immunoassay kit from Upjohn Corp. The films so obtained were immersed in distilled water at 20°C for 24 hours, then the water on their surface was removed, and the films were weighed to determined the water absorbency. The water absorbency was calculated by the following equation:

$$\text{water absorbency (\%)} = \{(W - D) / D\} \times 100$$

in which W is the weight of the film after immersion, and D is the dry weight of the film.

The results obtained are shown in Table 1. In this Table, the unit of the oxygen permeability coefficient is (cm^3 (STP) cm/cm^2.sec.cmHg).

[0035]

Table 1

		Oxygen permeability coefficient	Relative coagulation time	Complement activity			Water absorbency
		($X 10^{-8}$)	(glass = 1.0)	CH_{50} (%)	C3a	C5a	(%)
Examples	base polymer A	3.35	3.00	94.0	350	200	0.12
	quaternised polymer A	3.78	3.45	100	200	120	1.20
	quaternised polymer A + heparin	3.65	>10	100	20	40	1.33
	base polymer B	3.07	2.78	95.0	345	180	0.15
	quaternised polymer B	3.12	3.11	99.0	195	132	0.76
	quaternised polymer B + heparin	3.00	>10	99.0	25	39	0.42
	base polymer C	3.00	2.50	93.0	360	210	0.11
	quaternised polymer C	2.95	2.77	100	210	135	0.53
	quaternised polymer C + heparin	3.10	>10	100	23	43	0.56
Comp. expls	base polymer D	3.07	2.78	95.0	345	180	0.15
	quaternised polymer D	2.97	2.50	98.0	220	150	7.17
	quaternised polymer D + heparin	2.88	>10	100	35	60	14.31
	base polymer E	<0.1	2.00	60.0	600	450	63.0
	quaternised polymer E	<0.1	1.57	55.0	750	450	90.0
	quaternised polymer E + heparin	<0.1	>10	75.0	300	200	90.0

[0032] [Example 2] 3-n-butyl-3-aza-1,5-pentanediol (8040 parts) and phosphorous acid (10.3 parts) were placed into an autoclave and the mixture was stirred and heated under a nitrogen stream at 200 ~ 230°C under constant pressure for 26 hours to allow the reaction to proceed while removing the water formed by distillation. Subsequently, the pressure was reduced at 230°C in 2 hours from 760 mmHg to 0.3 mmHg, and the reaction was continued for another 3 hours at 230°C under 0.3 mmHg. In this manner an aminopolyether polyol (b) with an OH value of 64.7 and a basic nitrogen value of 6.75 mmol/g was obtained. A polydimethylsiloxane (3240 parts), shown by the formula 3 and having a mean molecular weight of 1800, MDI (1195 parts), said polyaminoether polyol (773.4 parts), dibutyltin dilaurate (0.3 part) and 1,4-butanediol (191.1 parts) were dissolved in a mixed solvent of THF (3782 parts) and DMF (7564 parts), and were reacted under a nitrogen stream at 20°C for 1 hour. The mixture was raised to 40°C and the reaction was continued for another 20 hours. In this manner a base polymer solution B, with a solid content of 32% and a viscosity of 1800 poise (at 30°C), was obtained. This base polymer solution B was, in the same manner as described in example1, quaternised with hexyl iodide. The same procedures as described in example 1 were carried out to give a base polymer B, a quaternised film B and a heparinised film B. The contents of basic nitrogen of these products were, respectively, 1.08 mmol/g and 0.410 mmol/g. From these results the quaternisation yield was calculated to be approximately 62%. Using the same procedures as described in example 1, the oxygen permeability coefficients, the relative coagulation times, the complement activities and the water absorbencies were measured. The results are shown in Table 1.

[0037] [Example 3] 3-n-butyl-3-aza-1,5-pentanediol (8738 parts) and phosphorous acid (10.3 parts) were placed into an autoclave and the mixture was stirred and heated under a nitrogen stream at 200 ~ 230°C under constant pressure for 26 hours to allow the reaction to proceed while removing the water formed by distillation. Subsequently, the pressure was reduced at 230°C in 2 hours from 760 mmHg to 0.3 mmHg, and the reaction was continued for another 3 hours at 230°C under 0.3 mmHg. In this manner an aminopolyether polyol (C) with an OH value of 58.7 and a basic nitrogen value of 6.30 mmol/g was obtained. A polydimethylsiloxane (3240 parts), shown by the formula 3 and having a mean molecular weight of 1800, MDI (1195 parts), said polyaminoether polyol (827.3

parts), dibutyltin dilaurate (0.3 part) and 1,4-butanediol (191.1 parts) were dissolved in a mixed solvent of THF (3802 parts) and DMF (7604 parts), and were reacted under a nitrogen stream at 20°C for 1 hour. The mixture was raised to 40°C and the reaction was continued for another 20 hours. In this manner a base polymer solution C, with a solid content of 32% and a viscosity of 1830 poise (at 30°C), was obtained. This base polymer solution was, in the same manner as described in example 1, quaternised with hexyl iodide. The same procedures as described in example 1 were carried out to give a base polymer C, a quaternised film C and a heparinized film C. The contents of basic nitrogen of these products were, respectively, 1.08 mmol/g and 0.410 mmol/g. From these results the quaternisation yield was calculated to be approximately 62%. By the same procedures as described in example 1, the oxygen permeability coefficients, the relative coagulation times, the complement activities and the water absorbencies were measured. The results are shown in Table 1.

[0038] [Comparative example 1] The base polymer solution B was treated by the same procedures described in example 1 to give a base polymer B.[8] Furthermore, in the same manner as example 1, the base polymer was quaternised with ethyl iodide to give a quaternised film D and a heparinized film D. The contents of basic nitrogen of these products were, respectively, 1.08 mmol/g and 0.410 mmol/g. From these results the quaternisation yield was calculated to be approximately 82%. By the same procedures as described in example 1, the oxygen permeability coefficients, the relative coagulation times, the complement activities and the water absorbencies were measured. The results are shown in Table 1.

[0039] [Comparative example 2] Acrylonitrile (24 parts) and acrylamide (89 parts) were thoroughly mixed with dimethyl sulphoxide (126 parts). To this mixed solvent were added dodecyl mercaptan (0.2 part) (chain extender), and bromoform (polymerisation initiator), and the mixture was exposed to a 100 W high pressure mercury vapour lamp placed 10 cm from it for 7 hours. The solution undergoing photopolymerisation was then poured into a large quantity of methanol to give a base polymer (24.4 parts) as a precipitate. This base polymer (10 g) was dissolved in dimethyl sulphoxide (120 parts) and dimethylami-

[8] Translator's note: base polymer D?

noethyl methacrylate was added. Graft polymerisation was carried out by exposing the solution to the 100 W high pressure mercury vapour lamp placed 10 cm from it for 19 hours. The solution undergoing graft polymerisation was then poured into a large quantity of methanol to give a graft polymer (12.8 parts) as a precipitate. The graft polymer so obtained was dissolved in dimethyl formamide, and ethyl bromide was added to quaternise the polymer, which was then shaped into a film (E). Subsequently, by the same procedures as described in example 1, the oxygen permeability coefficients, the relative coagulation times, the complement activities and the water absorbencies were measured. The results are shown in Table 1.

[0040] It can be clearly seen from the results shown in Table 1 that the polymer (E) of comparative example 2, which does not contain the polysiloxane unit, is poorly gas permeable and activates complements. In contrast, the polymers of the examples suppress complement activation, and are highly gas permeable. The performance of the polymer (D) of comparative example 1 is, at this stage, inferior to that of the polymers described in the examples.

[0041] [Example 5][9] The heparin was eluted[10] from the heparinized films A to E obtained in examples 1 to 3 and comparative examples 1 and 2 by immersing the films in a physiological sodium chloride solution (200 ml), the salt being replaced everyday for 2 weeks. The relative coagulation times of these eluted films were determined and the results are shown in Table 2.

[0042]

Table 2

	Examples			Comparative examples	
immersion time (day/s)	A	B	C	D	E
1	>10	>10	>10	7.0	3.5
3	>10	>10	>10	2.8	2.0
5	>10	>10	>10	2.8	2.0
7	>10	>10	>10	2.8	2.0
10	>10	>10	>10	2.8	2.0
14	>10	>10	>10	2.8	2.0

[0043] It can be seen from the results shown in Table 1[11] that the polymers in which the two side chains, two alkyl groups, bonded to the quaternised nitrogen

[9] Translator's note: Example 4 is missing.
[10] Translator's note: Literally "The heparinized films were eluted ..."

atom have a total number of carbon atoms ranging from 7 to 16, have a low water absorbency, and retain good hemocompatibility after being immersed[12] in a physiological sodium chloride solution for 2 weeks, while the polymers in which the two side chains, two alkyl groups, bonded to the quaternised nitrogen atom have a total number of carbon atoms of less than 6 have a high water absorbency. As the heparin is rapidly eluted from the polymers of the comparative examples the effect of heparin becomes practically nil after a 3-day immersion, and the polymers coagulate. It can be clearly concluded from the aforementioned results that the polymers according to the invention exhibit an excellent gas permeability and hemocompatibility.

[0044]

[Effect of the invention] The polyurethane or polyurethane urea according to the invention suppresses complement activation, exhibits good gas permeability and retain hemocompatibility over extended periods of time. For these reasons they are excellent materials to use in lung-heart machines, artificial lungs, ECMO, and so on.

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[11] Translator's note: Table 2?
[12] Translator's note: literally "eluted".